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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/325,603	06/03/1999	ALLAN SVENDSEN	4394.214-US	3011

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EXAMINER

SLOBODYANSKY, ELIZABETH

ART UNIT	PAPER NUMBER
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1652

35

DATE MAILED: 10/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/325,603

Applicant(s)

SVENDSEN ET AL.

Examiner

Elizabeth Slobodyansky

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 July 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 81,83,87-92 and 94-99 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 81,83 and 87-92 is/are allowed.
- 6) ☒ Claim(s) 94-99 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

The amendment filed on July 28, 2003 canceling claim 93 and adding claims 94-99 has been entered.

Claims 81, 83, 87-92 and 94-99 are pending. Claims 81, 83 and 87-92 have been allowed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 94-99 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 94(a) recites "three-dimensional structure [that] has at least three calcium binding sites". While the specification has support for the structure that "exhibits four calcium -binding sites" (page 9, lines 31-32), the examiner is unable to locate adequate support in the specification for the structure with "at least three calcium binding sites". Thus there is no indication that structures comprising at least three calcium binding

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sites were within the scope of the invention as conceived by Applicants at the time the application was filed. Claims 95-99 are rejected as dependent from claim 94.

Accordingly, Applicants are required to cancel the new matter in the response to this Office Action.

Claims 94-99 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for producing a variant of a parent α -amylase with an altered property having an amino acid sequence that is at least 70%, 75%, 80%, 85%, 90% or 95% homologous to the sequences of SEQ ID NOs: 2, 4 or 6 comprising the step of generating a model of said parent α -amylase using a three-dimensional structure of α -amylase having the amino acid sequence of SEQ ID NO:13 (Appendix 1), does not reasonably provide enablement for a method for producing a variant of a parent α -amylase having an altered requisite property comprising the step of generating a model of said parent α -amylase based on the structural properties listed in the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of

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direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Factors pertinent to this discussion include predictability of the art, guidance in the specification, breadth of claims, and the amount of experimentation that would be necessary to use the invention.

The specification teaches the three-dimensional structure of Termamyl-like α -amylase of SEQ ID NO: 13 (Appendix 1). SEQ ID NO:13 is made up of residues 1-300 of SEQ ID NO:2 and residues 301-483 of SEQ ID NO:4 (page 7, lines 15-28).

Therefore, these sequences are homologous to SEQ ID NO:13 in extent of 70%.

The specification discusses the use of computer to build the models of *B. licheniformis* α -amylase (TERM, SEQ ID NO:2) and *B. amyloliquefaciens* (BAN, SEQ ID NO:4) based on the structure of SEQ ID NO: 13 having coordinates shown in Appendix 1 (pages 62-63, Example 1). It further discloses the V54W and V54W/A52W mutants of SEQ ID NO:2 with an altered substrate cleavage pattern (pages 65-66). While the specification teaches a three-dimensional model of highly homologous Termamyl-like alpha-amylases based on the structure shown in Appendix 1, there are no examples of models built by using modeling computer programs based only on the structural properties listed in claim 94. There are no examples of the use of a computer

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generated model of a parent α -amylase based on another model for producing a variant thereof with an altered requisite property.

The state of the art allows to build three-dimensional structural model of an α -amylase based on the known structure. It is known in the art that even the availability of a three-dimensional structure does not necessarily make it possible to predict the effects of specific amino acid changes. However, knowing the structure/function relationship for the known α -amylase structure, it is possible to attempt to predict which residues should be mutated in a highly homologous parent α -amylase in order to alter a requisite property. Such prediction while not absolute is reasonably reliable. However, the reliability of such prediction dramatically declines, if possible at all, when a parent α -amylase structure is not a real structure but a model build on another model. There is no way to reliably correlate the structure/function relationship in an α -amylase with a known three-dimensional structure with a structure/function relationship in an α -amylase model built not on said known structure but on another model.

Therefore, while it is possible to build a model structure, one of ordinary skill in the art would require a guidance, beyond that provided, to predict what residues should be mutated in said model structure in order to alter the requisite property in a manner reasonably correlated with the scope of the claim. Without such guidance, the experimentation left to those skilled in the art is undue.

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The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 94-99 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 94(a) recites "wherein said model displays the coordinates for the three-dimensional structure". Model by itself does not display the coordinates. It is unclear whether the use of some special program is implied for that purpose. It further recites "connectivity -1, +3, -1X, and +2". Neither the term "connectivity" as a whole nor "connectivity -1, +3, -1X, and +2" are defined in the specification (page 9, lines 3-7). Further, it is unclear how computer is programmed to generate the requisite model without using a known structure. Therefore, claim 94 appears to be incomplete as missing the structure on which a model is built.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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Claims 94-99 are rejected under 35 U.S.C. 102(b) as being anticipated by Holm et al.

Holm et al. teach computer generated three-dimensional structural model of *B. stearothermophilus* based on the structure of Taka amylase A. They teach that in said *B. stearothermophilus* structure (SEQ ID NO:6 in this application), residues 1-104 and 208-400 belong to domain A, residues 105-207 to domain B and residues 401-515 to domain C (page 187, legend to Table II). This corresponds to residues 1-103 and 206-395 of SEQ ID NO:2 (domain A), residues 104-205 of SEQ ID NO:2 (domain B) and residues 396-483 of SEQ ID NO:2 (domain C) as required by claim 94(a) (specification, page 8, lines 1-3). They identified catalytic residues D331, D234 and E264 (page 187). Said residues correspond to D323, D231 and E261 in SEQ ID NO:2 (page 8, lines 5-6). They produced catalytically inactive mutants such as D331A, D234G and E264D as well as other mutants with altered catalytic properties by modifying the nucleotide sequence encoding *B. stearothermophilus* α -amylase and expressing said sequence in *E. coli* (page 181, last paragraph, through page 182, second paragraph; pages 186-187, Table II). Absent evidence to the contrary, the *B. stearothermophilus* structure comprises at least three calcium binding sites and one sodium binding site. Claims 94-99 do not require the model to be built on the structure of SEQ ID NO:13. Therefore, the teachings of Holm et al. anticipate claims 94-99.

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Response to Arguments

Applicant's arguments filed July 28, 2003 have been fully considered but they are not persuasive.

Applicants argue that "the present inventors determined the first actual three-dimensional structure of a Termamyl-like bacterial alpha-amylase as shown in the specification. Surprisingly, this structure was found to have, among other unique features, a special domain structure in loop 3 of the A domain. This special domain structure the B domain was previously unknown and not suggested in the art" (Remarks., page 9, 3rd paragraph). While Applicants determined the first actual three-dimensional structure of a Termamyl-like bacterial alpha-amylase, it appears that B-domain and its location were known (e.g., Holm et al., *supra*, and page 181, paragraph bridging two columns). Applicants argue that "the crux of the present invention is, that an artisan can readily provide a suitably accurate three-dimensional model structure of an enzyme, just as soon as the first actual detailed information about the three-dimensional structure of a sufficiently homologous enzyme becomes available. For example, when the unique three-dimensional structure of the Termamyl-like alpha-amylase of SEQ ID NO:13 was identified, it immediately became possible for the artisan to build reliable three-dimensional models of homologous Termamyl-like alpha-amylases, e.g. based on the structure shown in Appendix 1, or on the other structural properties listed in the new claims submitted herewith, for instance by using modeling

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computer programs. The skilled artisan could then I turn use those models to modify the properties of said homologous alpha-amylases e.g. by standard methods of single-site amino acid substitution/deletion/addition.

Once the three-dimensional structure of the first Termamyl-like alpha-amylase was solved by the instant inventors, solving subsequent homologous structures became a routine straightforward task for the skilled artisan” (page 10). These arguments are unpersuasive. While it is possible to build three-dimensional models of homologous Termamyl-like alpha-amylases based on the structure shown in Appendix 1, claims 94-99 are drawn not to modeling *per se* but to producing a variant with altered properties. The specification does not teach actual mutants of even SEQ ID NO: 13. It provides only potential locations mutations at which may result in changes in various properties of SEQ ID NO:13. With one exception, *supra*, it still has to be proven whether proposed mutations would result in desirable changes in properties. However, as discussed above, such predicted changes are deemed reasonable and, therefore, enabled. However, the transfer of structure/property correlation of actual structures such as SEQ ID NO:13 to model structures is unpredictable. In other words, it is possible to build a model based on another model but it would be unknown which residues to change in order to alter the requisite property.

Applicants further argue that “Applicants have provided a specific example in which a three-dimensional model of an alpha-amylase which was not SEQ ID NO:13

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was provided. See, e.g., Example 1 for *B. licheniformis* alpha-amylase" (page 11, lines 1-3). This is unpersuasive because Example 1 concerns with the computer built models of *B. licheniformis* α -amylase (SEQ ID NO:2) and *B. amyloliquefaciens* (SEQ ID NO:4) based on the structure of SEQ ID NO: 13 having coordinates shown in Appendix 1 (pages 62-63, Example 1). SEQ ID NO:13 is made up of residues 1-300 of SEQ ID NO:2 and residues 301-483 of SEQ ID NO:4, *supra*. Applicants used said models to produce the V54W and V54W/A52W mutants of SEQ ID NO:2, residues 52 and 54 of SEQ ID NO:2 are present in SEQ ID NO:13. Therefore, identifying residues to be changed in SEQ ID NO: 2 compared to the structure of SEQ ID NO:13 was not required. The V54W and V54W/A52W mutants can not be considered as an example sufficient to enable changes in other models. Therefore, the prediction as to which changes should be made in a model structure to result in the specific property is deemed unreliable based on the instant disclosure.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.



Elizabeth Slobodyansky, PhD
Primary Examiner

October 16, 2003